UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,626	06/27/2003	Stephen M. Kelsey	P1467R2P2	4813

9157 7590 03/29/2006

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
SANG, HONG	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 03/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/608,626	KELSEY ET AL.	
	Examiner	Art Unit	
	Hong Sang	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *7-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/27/03, 1/27/04 &.* 8/26/04, 11/5/04, 8/1/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

RE: Kelsey

1. Applicant's election of species medulloblastoma in the reply filed on 1/23/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. The information disclosure statements (IDS) filed on 6/27/2003, 1/27/2004, 8/26/2004, 11/5/2004 and 8/9/2005 have been considered. Signed copies are attached hereto.

3. Claims 1-12 are currently pending.

4. Due to species election, claims 1-5 are examined to the extent that the cancer is medulloblastoma. Claims 7-12 are withdrawn from further consideration as being drawn to non-elected species.

5. Claims 1-6 are under examination.

6. Because the applicants' elected species "medulloblastoma" is free of art. The search has been extended to the next species "carcinoma". Claims 1-5 are examined to the extent that the cancer is a carcinoma or medulloblastoma.

Priority

7. Applicant's claim for domestic priority under 35 U.S.C. 119(e) and under 35 U.S.C. 120 is acknowledged. However, applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and under U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The instant claims are drawn to method for treating medulloblastoma. All earlier filed applications upon which priority is claimed disclose a method for treating glioblastoma. The provisional application 60/141,316 and 10/268,501 also disclose a method for treating neuroblastoma. However, there is no disclosure of medulloblastoma. Accordingly, the claims, drawn to method of treating medulloblastoma, are given the priority date of current filing date 6/27/2003.

If applicant believes that support for medulloblastoma is present in the earliest filed priority document, applicant must, in responding to this action, point out with particularity, where such support may be found.

Specification

8. The specification is objected to because there is no brief description for Figure 8B and Figure 8C under the "Brief Description of the Drawings" (see page 7, line 10), however, the Drawings show Figure 8B and Figure 8C.

Claim Rejections - 35 USC § 112, 2nd paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 3-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-5 are rejected as vague and indefinite for reciting the terms 2C4 and 4D5 as the sole means of identifying the claimed molecules. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify 2C4, and 4D5, for example, by SEQ ID NO. or deposit of the hybridoma producing the antibody.

Claim Rejections - 35 USC § 112, 1st paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 3-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the

specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

Claims 3-5, and 12-14 recite specific antibodies 2C4, and 4D5 as part of the claimed invention. It is apparent that the recited antibodies are required to practice the claimed invention, because they are specifically required in the claims. As required elements they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the cell lines listed in claims 3-5, 8 and 12-14. See 37 CFR 1.802.

While the specification discloses on page 51 that the cell lines for 2C4, and 4D5 have been deposited with ATCC as HB-16797, CRL10463 (page 15, line 4), and CRL-2253", respectively, the specification does not indicate the terms of the deposit.

Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar

properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species 2C4, 4D5 and CP-358774. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority

and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

13. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQZd 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of treating medulloblastoma that expresses ErbB2 comprising administering a therapeutically effective amount of an antibody which binds ErbB2 to a patient. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass delivery of an anti-ErbB2 antibody to human brain.

Quantity of experimentation

The quantity of experimentation in the areas of cancer immunotherapy is extremely large given the unpredictability associated with cancer treatment, the lack of correlation of in vitro findings to in vivo success, animal study to human treatment. It would require significant study to determine which of the anti-ErbB2 antibody are in fact capable of crossing the brain blood barrier and reach the tumor at sufficient concentration for treating. The identification and characterization of each of these antibodies would be inventive, unpredictable, and difficult in itself, requiring years of inventive effort with no guarantee of success in doing so.

The unpredictability of the art and the state of the prior art

The prior art teaches a method of treating a carcinoma selected from the group consisting of human breast, renal, gastric and salivary gland carcinomas using an anti-ErbB2 antibody that binds specifically to the extracellular domain of the HER2 receptor (see US Patent No. 5,770,195, claims 1-6, IDS). The prior art does not teach a method of treating medulloblastoma using an anti-ErbB2 antibody.

Bickel et al. (Advanced Drug Delivery Reviews, 2001, 46: 247-279) teach that peptide and protein therapeutics are generally excluded from transport from blood to brain, owing to the negligible permeability of these drugs to the brain capillary

endothelial wall, which makes up the blood-brain barrier (BBB) in vivo (see abstract). Bickel et al. teach that at first glance, intraventricular administration via intrathecal catheters, connected to a subcutaneous drug reservoir, appears as a logical alternative to brain drug delivery, however, in addition to the invasive character of the procedure, additional pharmacokinetic considerations have to be taken into account (see page 250, right column, 2nd paragraph). Bickel et al. teach that while deep structures within the human brain cannot be reached by peptide or protein drugs administered via the intraventricular route, at the same time the surface of the brain is exposed to very high drug concentration with a steep gradient within the tissue (see page 252, 2nd paragraph). Bickel et al. teach that peptide or protein therapeutics may be delivered to the brain with the use of the chimeric peptide strategy for peptide drug delivery, e.g. a non-transportable peptide therapeutic is coupled to a BBB drug transport vector such as cationized albumin, or the OX26 monoclonal antibody to the transferring receptor (see abstract and pages 259 and 264). These proteins undergo absorptive-mediated and receptor-mediated transcytosis through the BBB, respectively. Bickel et al. teach that without solving the transcellular drug delivery problem, many drugs generated from a rational drug design approach for drug discovery will not be pharmacologically effective (see page 274, last paragraph).

Moreover, treatment of cancer in general is at most unpredictable. For example, Jain (Scientific American July 1994) discloses barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of

the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Moreover, treatment of cancer in a host is quite unpredictable. In addition, it was recently revealed that the drug Endostatin is unlikely to be the kind of across-the-board cancer cure that many had hoped for. Out of the 61 terminally ill patients tested, not one recovery had been seen (MSNBC News Services, "Mixed results on new cancer drug", November 9, 2000). Hence, it would not be predictable that a compound drawn to inhibiting cell proliferation would be effective in a host in need thereof- such as a host suffering from cancer. Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed,

since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. All of this underscores the criticality of providing workable examples in the specification, particularly in an unpredictable art such as cancer therapy.

Working examples

The specification teaches production and characterization of monoclonal antibody 2C4 (see example 1). The specification teaches humanized 2C4 antibodies (see example 3). The specification teaches a method of treating colorectal cancer with monoclonal antibody 2C4(see example 4). The specification teaches a method of treating colorectal, breast and lung cancer using humanized 2C4 (see examples 7, 12 and 13). The specification teaches pharmacokinetics, metabolism and toxicology of 2C4 (see example 8) and discloses that RhuMab 2C4 is stable in human serum. The specification teaches the dose of 2C4 antibody used for treating cancer patients (see example 9). The specification teaches intravenously administration of antibody to a subject (see Example 8). However, the specification fails to teach how to deliver the antibody to the brain tissue. There is no evidence indicating that the antibody e.g. 2C4, when administered intravenously, would be capable of crossing brain blood barrier and reaching the medulloblastoma so as to treat medulloblastoma as claimed. The specification provides little guidance to one of skill in the art in terms of how to use the

instantly claimed invention for the purposes of treating medulloblastoma. Therefore, coupled with the unpredictability of cancer treatment, particularly brain cancer treatment, using antibody, as underscored by the prior art, the criticality of providing workable examples in an unpredictable art, such as brain cancer immunotherapy, is required for the practice of the instant invention.

Guidance in the specification

The specification provides no specific or substantial guidance on the method of the delivery of the claimed antibody to brain. Without such guidance, one skilled in the art would not know how to practice the invention as claimed.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the method of the delivery of the antibody to brain and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1, 2, 3, and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/17797 (International Publication Date: 4/30/1998, IDS) as evidenced by Shepard et al. (J. Clinical Immunology, 1991, 11(3), 117-126, IDS).

A prior art search shows that a method for treating medulloblastoma using an anti-ErbB2 antibody is free of art. Therefore, the search has been extended to the next species "carcinoma". Accordingly, claims 1, 2, 3, and 5 are interpreted as a method of treating carcinoma that express ErbB2 comprising administering a therapeutically effective amount of an antibody which binds ErbB2 to a patient. The method is further limited wherein the antibody blocks ligand activation of an ErbB receptor, the antibody blocks binding of monoclonal antibody 2C4 to ErbB2, the antibody is monoclonal antibody 4D5 or humanized 4D5.

WO 98/17797 teaches a method of treating a tumor that overexpresses ErbB2 receptor comprising administering to a subject an effective amount of antibody such as 7C2, 7F3 and 4D5, wherein the tumor is carcinoma (see claims 28-31, page 36, lines 9-15). WO 98/17797 teaches that the antibodies 7C2, 7F3 and 4D5 bind to the extracellular domain of the receptor (see page 9, lines 22-30) and inhibit the ligand from binding the receptor (see column 5, lines 42-43).

The antibodies 7C2, 7F3 and 4D5 block ligand activation of an ErbB receptor and the antibody 7F3 blocks binding of monoclonal antibody 2C4 to ErbB2, as evidenced by Shepard et al.

Shepard et al. teach that the monoclonal antibodies 4D5, 2C4 and 7F3, etc. selectively bind the extracellular domain of ErbB2 (p185/HER2) and inhibit proliferation of human breast and ovarian tumor cells that express ErbB2 (see for example, Table III, page 123). Shepard et al. teach that the antibodies bind tightly to ErbB2, excludes ligand binding, downregulates receptor signaling pathways (see page 124, first paragraph). Shepard et al. teach that the antibody 7F3 blocks binding of monoclonal antibody 2C4 to ErbB2 (see notes of Table III, line 4).

16. Claims 1, 2 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Hudziak et al. (US Patent NO. 5,725,856, IDS).

Claims 1, 2 & 5 and their interpretation are set forth above (see paragraph 15).

Hudziak et al. teach a method of treating a patient having a carcinoma that overexpresses HER2 receptor comprising administering to said patient an antibody which binds specifically to the extracellular domain of the HER2 receptor in an amount effective to eliminate or reduce the patient's tumor burden (see claims 1 and 15-18), wherein the antibody is a monoclonal antibody 4D5 (ATCC CRL 10463) or a humanized antibody thereof (see claims 11 and 12). Hudziak et al. further teach that the antibody binds to the extracellular domain of the receptor and inhibit the ligand from binding the receptor (see column 5, lines 42-43).

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/17797 (International Publication Date: 4/30/1998, IDS) in view of Schaefer et al. (Oncogene, 1997, 15: 1385-1394, IDS), and as evidenced by Shepard et al. (J. Clinical Immunology, 1991, 11(3), 117-126, IDS).

The interpretations of claims 1, 2, 3, and 5 are set forth above (see paragraph 15).

Claim 4 embodies claim 1, wherein the antibody is monoclonal antibody 2C4 or humanized 2C4.

The teachings of WO 98/17797 and Shepard are set forth above as they apply to claims 1, 2, 3, and 5.

WO 98/17797 does not teach that the antibody is monoclonal antibody 2C4 or humanized 2C4. However, these deficiencies are made up for in the teachings of Schaefer.

Schaefer et al. teach that anti-ErbB2 monoclonal antibodies 2C4 and 4D5 inhibit proliferation of human breast cancer cells MDA-MB-175 and SK-BR-3 by blocking the association of ErbB2 with ErbB3 via blocking gamma-HRG activation of ErbB3 and

ErbB3 (Fig. 7). Schaefer et al. teach that these antibodies interfere with the ligand dependent formation of ErbB2-ErbB3 heterodimer complexes (see abstract, lines 20-24, and page 1390, 2nd paragraph)). Schaefer et al. teach that anti-ErbB23 monoclonal antibody 2C4 effectively blocks neuregulin binding and down stream signaling (see page 1390, left column, 2nd paragraph, lines 10-13). Moreover, Schaefer et al. teach that the antibody 2C4, which binds to a different ErbB2 epitope significantly inhibited (76%) cell growth in MDA-MB-175 cells, however, 4D5 shows only a moderate growth inhibition (see page 1390, left column, last section).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of WO 98/17797 by using 2C4 in the method of treating carcinoma because WO 98/17797 teaches a method of treating carcinoma using 7F3 antibody and 2C4 binds the same epitope as 7F3 does, as evidenced by Shepard et al. One would have been motivated to treat a carcinoma that expresses ErbB2 in a patient using a monoclonal antibody 2C4 in the method of WO 98/17797 because 2C4 has shown to be a more potent inhibitor than 4D5, for example in MDA-MB-175 cells. One of ordinary skill in the art would have a reasonable expectation of success to treat a carcinoma that expresses ErbB2 in a patient using a monoclonal antibody 2C4 in the method of WO 93/17797 because 2C4 and 7F3 are functional equivalent and bind same epitope of ErbB2 as evidenced by Shepard et al., and WO 93/17797 teaches a method of treating carcinoma using 7F3 antibody.

19. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak et al. (US Patent NO. 5,725,856, IDS) in view of Shepard et al. (J. Clinical Immunology, 1991, 11(3), 117-126, IDS) and Schaefer et al. (Oncogene, 1997, 15: 1385-1394, IDS).

The interpretations of claims 1- 5 are set forth above (see paragraphs 15 and 18).

The teachings of Hudziak are set forth above as they applied to claims 1, 2 and 5 (see paragraphs 16).

Hudziak does not teach the antibody blocks binding of monoclonal antibody 2C4 to ErbB2 and the antibody is monoclonal antibody 2C4 or humanized 2C4. However, these deficiencies are made up for in the teachings of Shepard et al. and Schaefer et al.

Shepard et al. teach that the monoclonal antibodies 4D5, 2C4 and 7F3, etc. selectively bind the extracellular domain of ErbB2 (p185/HER2) and inhibit proliferation of human breast and ovarian tumor cells that express ErbB2 (see for example, Table III, page 123). Schaefer et al. teach that the antibodies bind tightly to ErbB2, excludes ligand binding, downregulates receptor signaling pathways (see page 124, first paragraph). Schaefer et al. teach that the antibody 7F3 blocks binding of monoclonal antibody 2C4 to ErbB2 (see notes of Table III, line 4).

Schaefer et al. teach that anti-ErbB2 monoclonal antibodies 2C4 and 4D5 inhibit proliferation of human breast cancer cells MDA-MB-175 and SK-BR-3 by blocking the association of ErbB2 with ErbB3 via blocking gamma-HRG activation of ErbB3 and ErbB3 (Fig. 7). Schaefer et al. teach that these antibodies interfere with the ligand

dependent formation of ErbB2-ErbB3 heterodimer complexes (see abstract, lines 20-24, and page 1390, 2nd paragraph)). Schaefer et al. teach that anti-ErbB23 monoclonal antibody 2C4 effectively blocks neuregulin binding and down stream signaling (see page 1390, left column, 2nd paragraph, lines 10-13). Moreover, Schaefer et al. teach that the antibody 2C4, which binds to a different ErbB2 epitope significantly inhibited (76%) cell growth in MDA-MB-175 cells, however, 4D5 shows only a moderate growth inhibition (see page 1390, left column, last section).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat a carcinoma that express ErbB2 in a patient using a monoclonal antibody 2C4 or 7F3 instead of 4D5 in the method of Hudziak because Shepard et al teach both 2C4 and 7F3 inhibit proliferation of human breast and ovarian cancer cells in vitro. One would have been motivated to treat a carcinoma that express ErbB2 in a patient using a monoclonal antibody 2C4 or 7F3 instead of 4D5 in the method of Hudziak because 2C4 and 7F3 bind to a different epitope from 4D5 and 2C4 has shown to be a more potent inhibitor than 4D5, for example in MDA-MB-175 cells. One of ordinary skill in the art would have a reasonable expectation of success to treat a carcinoma that express ErbB2 in a patient using a monoclonal antibody 2C4 or 7F3 instead of 4D5 in the method of Hudziak because Hudziak teach a method of treating a carcinoma that express ErbB2 in a patient by a monoclonal anti-ErbB2 antibody and Schaefer teaches the monoclonal antibodies 2C4 and 7F3 that bind specifically to the same receptor ErbB2 inhibit proliferation of breast and ovarian cancer cells in vitro.

Double Patenting

20. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

21. Claims 1-5 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-5 of copending Application No. 10/268,501. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims 1-5 and their interpretation are set forth above (see paragraphs 15 and 18)

Claims 1-5 of copending Application No. 10/268,501 are drawn to a method of treating carcinoma that expresses ErbB2 comprising administering a therapeutically effective amount of antibody which binds ErbB2 to a patient. The method is further limited wherein the antibody is monoclonal antibody 4D5 or humanized 4D5, the antibody blocks ligand activation of an ErbB receptor, the antibody blocks binding of monoclonal antibody 2C4 to ErbB2, the antibody is monoclonal antibody 2C4 or humanized 2C4. Therefore, claims 1-5 of copending Application No. 10/268,501 claim the same invention as that of instant claims 1-5.

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 1 and 5 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 11, and 15-18 of US Patent No. 5,725,856, and over claims 1, 6, 11 and 13 of US Patent No. 5,770,195. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1 and 5 and their interpretation are set forth above (see paragraphs 15).

Claims 1, 11 and 15-18 of US Patent No. 5,725,856 are drawn to a method for of treating a patient having a carcinoma that overexpresses HER2 receptor comprising administering to said patient an antibody which binds specifically to the extracellular domain of the HER2 receptor in an amount effective to eliminate or reduce the patient's tumor burden, wherein said antibody has the identifying biological characteristics of

monoclonal antibody 4D5, the carcinoma is renal carcinoma, human breast carcinoma, gastric carcinoma and salivary glad carcinoma.

Claims 1, 6, 11 and 13 of US Patent No. 5,770,195 are drawn to a method of inhibiting the growth of tumor cells that overexpress HER2 receptor comprising administering to a patient an antibody which binds specifically to the extracellular domain of the HER2 receptor in an amount effective to inhibit the growth of the tumor cells in the patient, wherein the tumor cells comprises a carcinoma selected from the group consisting of human breast, renal, gastric and salivary gland carcinomas, said antibody has the identifying biological characteristics of monoclonal antibody 4D5.

Therefore, claims 1, 17 and 22 of the US Patent No. 5,725,856 and claims 1, 6, 11 and 13 of US Patent No. 5,770,195 anticipate the instant claims 1 and 5.

Claims 1 and 5 directed to an invention not patentably distinct from claims 1, 11 and 15-18 of commonly assigned US patent No. 5,725,856 and from claims 1, 6, 11 and 13 of US Patent No. 5,770,195 for the reasons set forth above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned US Patent Nos.5,725,856 and 5,770,195, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions

were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

24. Claims 1 and 5 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 11, and 15-18 of US Patent No. 6,627,196B1. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1, 5 and their interpretation are set forth above (see paragraphs 15).

Claims 1, 17 and 22 of US Patent No. 6,627,196B1 are drawn to a method for treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising administering an effective amount of an anti-ErbB2 antibody to the human patient, comprising administering to the patient an initial dose of at least approximately 5mg/kg of the anti-ErbB2 antibody, and administering to the patient in an amount that is approximately the same or less than the initial dose, wherein the subsequent doses are separated in time from each other by at least two weeks, wherein the cancer is endometrial carcinoma, salivary glad carcinoma, hepatic carcinoma, the antibody is a humanized 4D5 anti-ErbB2 antibody. Therefore, claims 1, 17 and 22 of the US Patent No. 6,627,196B1 anticipate the instant claims 1 and 5.

Claims 1 and 5 directed to an invention not patentably distinct from claims 1, 17 and 22 of commonly assigned US patent No. 6,627,196B1 for the reasons set forth above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned US Patent No.6,627,196B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Claim Rejections - 35 USC § 102

25. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(f) he did not himself invent the subject matter sought to be patented.

26. Claims 1-5 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The interpretation of claims 1-5 is set forth above (see paragraphs 15 and 18 above).

Claims 1, 11 and 15-18 of US Patent No. 5,725,856, claims 1, 6, 11 and 13 of US Patent No. 5,770,195, claims 1, 17 and 22 of US Patent No. 6,627,196B1 and claims 1-5 of the copending Application No. 10/268,501 anticipate the instant claims 1-5 for the reasons set forth above (see paragraphs 21, 23 and 24).

Claims 1-5 directed to an invention not patentably distinct from claims 1, 11 and 15-18 of commonly assigned US Patent No. 5,725,856, claims 1, 6, 11 and 13 of US Patent No. 5,770,195, claims 1, 17 and 22 of US patent No. 6,627,196B1 and claims 1-5 of the copending Application No. 10/268,501. The inventors for US Patent No. 5,725,856 are Hudziak, Ullrich and Fendly, for US Patent NO. 5,770,195 are Hudziak, Shepard, Ullrich and Fendly, for US Patent No. 6,627,196B1 are Baughman and Shak, and for the copending Application No. 10/268,501 are Sliwkowski. Because of the rejections above (see paragraphs 21, 23 and 24), one would conclude that it is the inventors for US Patent No. 5,725,856, 5770,195 and 6,627,196B1 who invented the claimed subject matter. Moreover, the copending Application No. 10/268,501 claims the same subject matter as the instant application and Slikowski is the sole inventor for 10/268,501, however, the inventors for the instant application are Slikowski and Kelsey, therefore it is unclear who invented the instant subject matter.

Conclusion

27. No claims are allowed.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hong Sang
Art Unit 1643
Jan. 12, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER